UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/063,978	04/21/1998	ROBERT J. OBREMSKI	45D-1750(641	5283

7590 12/13/2001

BECKMAN COULTER, INC.
4300 N. HARBOR BLVD
P.O.BOX 3100
FULLERTON, CA 92834-3100

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 12/13/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/063,978	Applicant(s) OBREMSKI ET AL	
	Examiner Ja-Na A Hines	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 October 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attached comments*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-28*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

ADVISORY ACTION

1. Claims 1-28 are pending in this office action.

Response to Arguments

2. Applicant's arguments filed October 15, 2001 have been fully considered but they are

not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The rejection of claims 1-4, 13-19, 21 and 23-28 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) is maintained for reasons previously set forth. The rejection was on the grounds that it would have been obvious, at the time of applicants invention to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (J. of Clinical Immun.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

Applicant argues that the microscopic sorbent zones unexpectedly deplete substantially all analyte from the sample and concentrate the analyte onto the small measurement region. Applicant also states that there is an unexpected benefit of high signal-to-background ratio of binding assay by concentrating the signal on the small area of support.

However, it is the examiner's position that Ekins et al., (EP 304,202) teach small sample sizes in individual micro-arrays wherein the concentration of binding reagent may range from 10^5 to 10^{10} molecules of binding agent. Understanding that the

recognition of such small amounts of binding agents is permissible, next it is feasible to place the binding agent required for a single concentration measurement on a very small area of a solid support. A high coating density is generally desirable to maximize signal/noise ratios. Ekins et al., (J. of Clinical Immuno.) teach measuring the analyte concentration in the medium to which the antibody is exposed wherein the analyte binding by antibody clearly causes analyte depletion in the surrounding medium. Therefore, Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach microscopic sorbent zones that unexpectedly deplete substantially all analyte from the sample and concentrate the analyte onto the small measurement region. Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach using large amounts of antibody to capture analyte in a small sample, which substantially deplete the sample of analyte.

Applicants urge that both references require only an insignificant proportion of any analyte present in the liquid sample becomes bound to the binding agent, and that the references teach away from analyte depletion. It is the examiner's position that Ekins et al., (J. of Clinical Immuno.) teach antibody binding of an analyte clearly causes analyte depletion in the surrounding medium (page 173 para. 1). The figure shows antigen bound concentrations as high as 100% when using higher antibody concentration. The instant specification defines substantial depletion to be at least about 60% of analyte. Thus, Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach substantial analyte depletion as defined by the instant application.

Applicants argue that it is unexpected that microscopic sorbent zones can substantially deplete analyte from a macroscopic, 100ul, sample volume and is not

obvious to one of skill in the art. Ekins et al., (EP 304,202) teach sample sizes of the order of one or a few milliliters, i.e., from about 100ul or less, however circumstances may arise when larger volumes are assayed and the geometry can be adjusted (page 6 lines 27-29). Example 1 teaches the spots on the support are approximately $1mm^2$ and a sample volume of about 400ml or 2.4×10^{10} molecules of analyte. Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (J. of Clinical Immun.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

Applicants argue that their assay is drawn to a binding assay for sensing analyte mass, whereas the references teach analyte concentration. However, the references teach the same method steps, use the same laser microscopy techniques to assay the analyte, and provide results in terms of molecules bound. Applicant use of analyte mass appears to be identical to the prior art's reference to analyte concentration. The laser analysis of applicants analyte mass does not provide the weight of the analyte, but provides the concentration, just as the prior art references. Therefore, applicants argument that the assays are providing different measurements is unpersuasive.

4. The rejection of claims 1-4, 13-19, 21 and 23-28 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (Analytica Chimica Acta.) is maintained essentially for reasons set forth in the previous office action. Ekins et al., (EP 304,202) teach the limitations, i.e., an insoluble support and the binding capacity of the microscopic sorbent zone is 150um and is about 10^{10} analyte molecules, of claims 27-28.

No more than routine skill is required to implement well-known techniques such as analyte depletion into the binding assay of Ekins et al. (EP 304,202). Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (Analytica Chimica Acta.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

Applicants argue that the combination of references does not teach substantial depletion of the analyte from the sample. However, Ekins et al., (EP 304,202) have been discussed above. Therefore, Ekins et al., (EP 304,202) in view of Ekins et al., (Analytica Chimica Acta.) teach substantial depletion of analyte in the surrounding medium. See the previous discussions.

5. The rejection of claims 5-10 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) and either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.), in further view of Ullman et al., (US Patent 5,512,659) is maintained for reasons already of record. Ekins et al.(EP 304,202), Ekins et al., (J. of Clinical Immuno.) and Ekins et al., (Analytica Chimica Acta.) have been discussed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious at the time of applicants invention to have used the first binding partner,

conjugate, biotin-avidin labels and biotinylated antibodies as taught by Ullman et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Ullman et al., teach that these methods are more versatile and convenient than the known methods.

6. The rejection of claim 11 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in further view of Waggoner et al., US Patent (5,368,486) is maintained for reasons of record.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. No more than routine skill would have been required to use cyanine dyes as taught by Waggoner et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Waggoner et al., teach that these cyanine dyes are intrinsically more fluorescent; have improved photostability; improved water solubility; can label a wide variety of biological materials; and subject to a variety of excitation wavelengths using lasers.

7. The rejection of claim 12 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Waggoner et al., US Patent (5,368,486) in further view of Lee et al., (US Patent 5,453,505) is maintained. In this case, applicants

argue that there is no suggestion to combine the references, however the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Lee et al., teach the most stable dye was found to be the dye with the shortest wavelength, Cy5 whose structure contains five methine groups, while the remaining dyes contain seven methine groups, such as Cy7 that has similar stability. Accordingly, it would have been obvious at the time of applicants invention to have used Cy5 or Cy7 as taught by Lee et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.), and Waggoner et al., US Patent (5,368,486), because Lee et al., teach a reduced tendency to aggregate and enhanced photostability.

8. The rejection of claim 20 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Northrup et al (US Patent 5,639,423) is maintained. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, it would have been obvious at the time of applicants invention to use the well known method of dispensing material using a jet printer as taught by Northrup et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al.,

(J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Northrup et al., teach that the method is especially advantageous for biochemical reactions.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines
December 5, 2001

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600